Surveillance of Antibiotic Prescribing Practices and Trends of Resistance at a Private Hospital in Zimbabwe.

by
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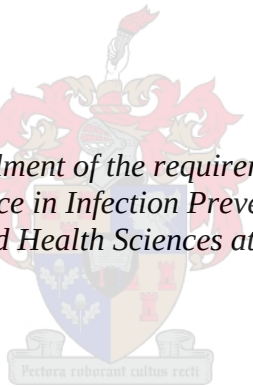

Thesis presented in fulfilment of the requirements for the degree of
Master of Science in Infection Prevention Control
in the Faculty of Medicine and Health Sciences at the Stellenbosch University

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March 2020

DECLARATION

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ABSTRACT

INTRODUCTION

Antibiotic resistance is a world-wide burden characterised by inappropriate prescribing practices, poor surveillance systems and poor laboratory capacity in the low income countries. Antibiotic prescribing practices relates to the way clinicians give antibiotics as treatment of infections. Monitoring of prescribing practices is of paramount importance so as to know the currents patterns, raise awareness on antibiotic usage and to create opportunities for antibiotic stewardship programmes. This study on surveillance of prescribing practices and trends of resistance at this facility in Zimbabwe is to raise awareness on antibiotic usage and to create an opportunity for antibiotic stewardship programmes.

METHODOLOGY AND RESULTS

In the course of the study 220 patients had their prescriptions reviewed for antibiotic prescribing patterns it was observed that Ceftriaxone was the most drug prescribed 176 patients got Ceftriaxone. Most patients got more than one antibiotic and 18 of the 220 got 5 antibiotics. A questionnaire was administered to 50 of the doctors who admit at this private healthcare facility to assess which guidelines they use to prescribe antibiotics. However, 32% responded to the questionnaire and most of the doctors do not use national guidelines but other guidelines to prescribe antibiotics. Microbiological data from blood cultures were reviewed from 2011-2015 to assess common pathogens and their susceptibility pattern. Total of 845 samples were reviewed 667 had no growth, 36 were contaminated and 142 had susceptibility results. The most common organism with resistance to almost all antibiotics tested was coagulase negative staphylococci and with a highest percentage of resistance to Cloxacillin at 89.09%.

CONCLUSION

Development of a surveillance system to monitor prescribing practices and reporting of resistance patterns in low income countries healthcare facilities will reduce antibiotic resistance as it adds data to the national health systems and assist in the development of national antibiotic policy and antibiotic stewardship programmes.

OPSOMMING

Agtergrond

Weerstand teen antibiotika is ‘n wêreld-wye las, wat gekarakteriseer word deur onbehoorlike voorskryf-praktyke, swak waaktoesigsisteme en swak laboratoriumkapasiteit in die lae-inkomste lande. Antibiotiese voorskryf-praktyke hou verband met die manier waarop klinici antibiotika as behandeling vir infeksies gee. Die monitering van voorskrywingspraktyke is van uiterse belang om die huidige patrone te ken, bewustheid te wek oor die gebruik van antibiotika en om geleenthede te skep vir programme vir die bestuur van antibiotika. Hierdie studie dek die waaktoesig oor voorskrywingspraktyke en weerstandigheid by die fasiliteit in Zimbabwe. Dis om bewustheid oor die gebruik van antibiotika te vermeerder en om 'n geleentheid te skep vir programme vir bestuur van antibiotika.

Metodologie en resultate

Gedurende die studie was 220 pasiënte se voorskrifte ondersoek vir antibiotiese voorskrifpatrone. Keftriaksoon was die meeste voorgeskryf: 176 pasiënte het Keftriaksoon gekry. Die meeste pasiënte het meer as een antibiotika ontvang, en 18 van die 220 het 5 antibiotika ontvang. 'n Vraeboog is aan 50 dokters wat pasiënte in hierdie privaat gesondheidsorg-fasiliteit opneem gegee om te bepaal watter riglyne hulle gebruik om antibiotika voor te skryf. Die vraeboog is deur 32% voltooi. Die meeste dokters gebruik nie die nasionale riglyne nie, maar ander riglyne om antibiotika voor te skryf. Mikrobiologiese data van bloedkulture is vanaf 2011-2015 hersien om algemene patogene en hul sensitiviteitspatrone te bepaal. Altesaam 845 monsters is beoordeel, waarvan 667 geen groei gehad het nie, 36 gekontamineerd was en 142 sensitiviteitsresultate gehad het. Die algemeenste organisme met weerstand teen byna al die antibiotika wat getoets is, was koagulase-negatiewe stafilokokke en met 'n hoogste persentasie weerstand van 89,09% teen Cloxacillin.

Gevolgtrekking

Die ontwikkeling van 'n waaktoesigstelsel om voorskrywingspraktyke te monitor en verslagdoening oor weerstandspatrone in gesondheidsorgfasiliteite in lae-inkomstelande sal antibiotiese weerstandigheid verminder, aangesien dit data tot die nasionale gesondheidstelsels toevoeg en help met die ontwikkeling van nasionale antibiotika-beleid en programme vir die bestuur van antibiotika.

ACKNOWLEDGEMENTS

I would like to thank Professor VJ Robertson and Doctor Jack Meintjes for all their effort in guiding and encouraging me throughout this study.

My gratitude also goes to Mrs. Anna Maruta my mentor for inspiring me to pursue the Master Degree in infection control.

Special mention goes to PSMI management and Westend hospital management for allowing me to carry out this study at their facility.

I also want to thank Mrs. Petronella Shayamano and Mr. Lovemore Chipindu for assisting me with statistical analysis.

Lastly I would want to thank my husband Pumulani Musagwiza, son Tapiwanashe and daughter Mazvita for encouragement and moral support during the course of this study.

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List of Abbreviations

AIDS	Acquired Immuno-Deficiency Syndrome
AMR	Antimicrobial Resistance
EDLIZ	Essential Medicine List and Standard Treatment in Zimbabwe
GARP	Global Antibiotic Research and Development Partnership
GLASS	Global Antimicrobial Resistance Surveillance System
HDU	High Dependence Unit
HIV	Human Immunodeficiency Virus
IACG	Interagency Coordinating Group on AMR
ICU	Intensive Care Unit
MCAZ	Medicines Control Authority of Zimbabwe
NNU	Neonatal Unit
PSMI	Premier Service Medical Investments
STI	Sexually Transmitted Infection
TB	Tuberculosis
UK	United Kingdom
USA	United States of America
WHA	World Health Assembly
WHO	World Health Organisation

CHAPTER ONE: INTRODUCTION

Antibiotic resistance occurs when an antibiotic loses its ability to effectively control or destroy bacterial growth during an infection hence bacteria will continue to cause infection despite the presence therapeutic levels of the antibiotic. [1] Penicillin was discovered by Alexander Fleming in 1928, it was first used in the mid-1940s but by 1950 resistance had started to emerge. This is also the case for other antibiotics including the Sulphonamides discovered and used in the 1930s followed by resistance development in the 1940s.[1]Antibiotic resistance is a global challenge characterised by overuse of antibiotics in human and animal medicine and antibiotics are the most used drugs in healthcare.[2] In an effort to prevent and control antibiotic resistance the World Health Organisation (WHO) and many other international health bodies are developing policies on surveillance of antibiotic usage and resistance to be used by all countries in all continents to inform on what guidelines to be used to reduce resistance.[3]

The burden of antibiotic resistance is not well known in the African region as there is a paucity of data. There is lack of antibiotic surveillance systems in most African countries and therefore the extent of the problem is not well understood. Poor microbiological laboratory capacity also contributes to poor monitoring of trends of antibiotic resistance, hence the inadequate and inaccurate data.[4]Most data on antibiotic resistance is from developed countries such as United Kingdom (UK) and the United States of America (USA), and scanty or no data from developing countries. In Africa a few countries like Ghana, Kenya, South Africa and Tanzania have data on antibiotic prescribing practices and trends of resistance but Zimbabwe is one of the African countries with very little data .[5]

A study on antimicrobial resistance in gonococci isolates from patients and sex workers in Harare Zimbabwe was done by Mason et al. in 1997. This data is thus very old, but showed resistance of gonococcal infection to ceftriaxone.[6] Another study on prevalence and drug resistance in bacteria isolated from urinary tract infections in Bulawayo Zimbabwe was done by Mbanga in 2015 and found high resistance to Ampicillin (84%) and to Cotrimoxazole (68.5%) on Gram negative bacilli and resistance was also shown on coagulase – negative staphylococci (88.1%) on Nalidixic Acid and to Cotrimoxazole (69%).[7] A recent study on antibiotic resistance in bacterial pathogens causing meningitis in children at Harare Central

Hospital in Zimbabwe was done by Gudza -Mugabe in 2016 and it showed 100% resistance of *Strep-pneumoniae* to Cotrimoxazole and 40% resistance to Tetracycline.[8]

As there is a paucity of data on antibiotic prescribing practices and trends of resistance to guide empirical treatment there is a need to carry out more studies to address this gap. This study on surveillance of prescribing practices and trends of resistance at a private hospital in Zimbabwe will be of great importance as it will add to the existing data and investigate the gaps of lack of data on resistance patterns, lack of systems that monitors prescribing practices, lack of feedback to the clinicians on resistance patterns and failure of institutions to put in place enough staff in laboratories such that turnaround time of the results is not affected.

CHAPTER TWO: LITERATURE REVIEW

Antibiotic resistance

Antibiotic resistance occurs when an antibiotic loses its ability to destroy bacterial growth during an infection hence allowing them to grow despite therapeutic levels. [(1)] Antibiotic resistance contributes to increased morbidity, mortality and financial burden in healthcare systems. [(9)] The consequences of inappropriate antibiotic prescribing range from those which increase morbidity and mortality to those which increase financial burden to healthcare systems. Those that increase morbidity and mortality are prolonged disease process, colonisation, increased risk of spread of resistant organisms and poor patient outcomes leading to death. Those that increase financial burden to healthcare systems are increased cost of hospitalisation, advanced diagnostic tests and expensive broad spectrum antibiotics to treat the infection. [(10)]

Antibiotic resistance is a global threat due to inappropriate use of antibiotics in humans and in animals. There is a considerable rise in new resistance mechanisms making it difficult to treat common infections. The Centre for Disease Control (CDC) reported in 2017 that antibiotic resistance in Europe causes 25 000 deaths per year and 2.5 million extra days of staying in hospital and in the United States 23000 deaths and above 2 million illnesses are caused per year.[(10)] Antibiotic usage needs to be monitored to reduce resistance, different factors contribute to antibiotic resistance but the main ones are inappropriate prescribing practices, patients not finishing antibiotic course, overuse of antibiotics in animal husbandry and aquaculture, poor adherence to infection control practices, poor hygiene and sanitation and no discovery of new antibiotics.[(11)]

Extent of the problem in Zimbabwe

Antibiotic resistance is a global burden, and Zimbabwe has very little data on antibiotic prescribing practices and patterns of resistance. A study on antimicrobial resistance in gonococci isolates from patients and sex workers in Harare Zimbabwe was done by Mason et al in (1997). [6)] This data is thus very old, but it showed that at the time there was resistance of gonococcal infection to ceftriaxone. A later study on prevalence and drug resistance in bacteria isolated from urinary tract infections in Bulawayo Zimbabwe was done by Mbanga

in 2015 and found that there is high resistance to Ampicillin (84%) and to Cotrimoxazole (68.5%), in Gram negative bacilli and resistance was also shown by coagulase – negative staphylococci to Cotrimoxazole (69%).[7] A recent study on antibiotic resistance on bacterial pathogens causing meningitis in children at Harare Central Hospital showed that *Streptococcus pneumoniae* was totally resistant to Cotrimoxazole (100%)and resistant to Tetracycline (40%).[8]A review of the literature indicates a lack of studies on the burden of antibiotic resistance and the nature of prescribing practices in Zimbabwe. However, a WHO report indicates antimicrobial resistance in the treatment of Gonorrhoea, Cholera, Typhoid Tuberculosis, Malaria and HIV/AIDS infections. [12]

Strategies to reduce antibiotic resistance

As antimicrobial resistance(AMR) becomes a global threat, those infections that were once treated easily are no longer treatable. The World Health Assembly (WHA) approved a global action plan to address the problem in May 2015. Strategic objectives were set as follows:

- To improve awareness and understanding of AMR through effective communication, education and training
- To strengthen knowledge and evidence base through surveillance and research
- Reduce incidences of infection through effective sanitation, hygiene and infection prevention measures.
- Optimise use of antimicrobial medicines in humans and animals.
- Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions. [12]

The WHO also implemented activities to address the antibiotic issue in 2015, which include:

- World antibiotic week
- The global antimicrobial resistance surveillance system (GLASS)
- Global antibiotic research and development partnership (GARP)
- Interagency coordinating group on AMR (IACG)

The WHO launched a global action plan for every country to tackle antimicrobial resistance using the One Health Approach in October 2015. Zimbabwe adopted the One Health

Approach whereby multisectoral groups would work together to promote good health in humans, animals and the environment. The AMR Core Group was formed to tackle the problem of antimicrobial resistance in Zimbabwe. The group is composed of representatives from Ministry of Health, Ministry of Agriculture, Ministry of Environment, Water and Climate. In 2017 the AMR Core Group carried out point prevalence surveys in 18 healthcare facilities and factors such as prescribing antibiotics to common colds and diarrhoea that contribute to antibiotic resistance were identified. Hence the need to raise awareness and educate professionals, community and the policy makers on AMR. A situational analysis was done and a National AMR Action Plan was developed with 5 strategic objectives. [13] which are aligned to the WHO Global Action Plan as follows:

- Raise awareness and educate the population, professionals and policy makers on AMR.
- Improve understanding of the AMR burden and antimicrobial use patterns through surveillance.
- Reduce the need for antimicrobials by improving infection prevention and control, improved farm practices and biosecurity, water sanitation and hygiene, and immunisation.
- Improve controlled access and optimise the use of antimicrobials in humans and animals
- Sustainable investment into AMR and research

Surveillance of antibiotic resistance

The World Health Organisation (WHO) in its response to increasing antibiotic resistance showed in a worldwide country situational analysis that there is limited data on antibiotic usage and resistance in most of African countries and so it is difficult to determine the extent of the problem. [14] Studies have shown inappropriate prescribing of antibiotics globally by clinicians when trying to treat suspected infections. There is also inappropriate use of antibiotics in animal husbandry, where farmers mostly use antibiotics to promote animal growth instead of treating infection. [15] The WHO antimicrobial resistance global report on surveillance revealed bacterial resistance to some antibiotics on pathogens that causes infection are common worldwide. [2] (See table 1)

Table 1: List of common pathogens resistant to group of antibiotics (adopted from WHO Global Priority List of Antibiotic Resistant Bacteria) [(2)]

Bacteria	Antibiotics resistant
Escherichia coli	3rd generation cephalosporin and fluoroquinolones
Klebsiella pneumoniae	3rd generation cephalosporin and Cabarpenems
Staphylococci aureaus	Methicillin resistant
Non typhoidal salmonella	Fluoroquinolones
Shigella	Fluoroquinolones
Neisseria gonorrhoea	3rd generation cephalosporin

In the WHO communicable disease surveillance and response systems guide to monitoring and evaluation, "*surveillance"* is then defined as the ongoing systematic collection, analysis, and interpretation of outcome specific data for use in planning, implementing and evaluating public health policies and practice. [(3)]

Surveillance of antibiotic resistance involves collection of antibiotic susceptibility test results and must be based on standardised systems from the microbiology laboratory. Susceptibility test results, demographic and clinical data of the population with the identification of pathogens isolated will help to formulate an intervention that will reduce antibiotic resistance. Surveillance of antibiotic resistance is being implemented in many high income countries and WHO is calling for all countries including developing countries to introduce surveillance systems. [(13)]

Surveillance of antibiotic resistance is important to measure the size of the problem. In addition to the standardised testing, the surveillance system requires proper records, a system of data storage and feedback for the purpose of managing bacterial infections. Hospitals in Zimbabwe have no surveillance systems for monitoring antibiotic resistance and the general burden of resistance in hospitals has not been determined. However, surveys on specific infections like tuberculosis (TB), sexually transmitted diseases (STDs) and bacterial meningitis are done. In Kenya's situational analysis and recommendations on antibiotic use and resistance, it was recommended that surveillance of antibiotic usage and trends of antibiotic resistance is of paramount importance.[(5)] In Zimbabwe there is also limited data on

antibiotic usage, lack of systems that monitor clinicians prescribing practices, lack of personnel who are knowledgeable about surveillance of antibiotic usage and resistance, and lack of feedback to clinicians on resistance patterns are all contributing to poor management of antibiotics.[13]However, in Zimbabwe's National Action Plan, surveillance of antimicrobial resistance and antimicrobial usage is one of the strategic objectives. A general survey of knowledge attitude and practice amongst animals and human health professionals, and a point prevalence survey in18 hospitals was carried out in 2017. [13] The results showed inappropriate antimicrobial use and varied knowledge of antimicrobial resistance. Therefore, education and awareness on antimicrobial resistance, auditing of antimicrobial usage, feed back to the clinicians, and adherence to infection control practices are of paramount importance [14]

Antibiotic Prescribing Practice

Antibiotic prescribing practice describes the way clinicians use antibiotics to treat infections through knowing the diagnosis, giving the correct drug, dose, by the correct route and knowing the side effects and contraindications. [18] It is of paramount importance to investigate antibiotic prescribing practices to understand the current patterns. Monitoring of antibiotic use is also important as it will raise awareness of inappropriate antibiotic usage and give an opportunity to provide guidance to improve prescribing practices. Akande et al (2009) in their study at a tertiary university hospital in Nigeria investigated antibiotic prescribing patterns and cost. They found that more antibiotics were prescribed to out-patients than in-patients. Elderly patients had more than one antibiotic prescribed and had a longer duration than the younger patients. The author concluded that it is important to monitor antibiotic prescribing practices in developing countries because if not monitored, it increases the healthcare cost such as increased hospital bills due to the number of antibiotics prescribed and the duration of the drug usage. [17]

In Zimbabwe bacterial infections are often treated empirically whilst waiting for culture results, because of poor laboratory capacity, culture results take time to reach the clinicians and hence affecting the prescribing practice in both private and government healthcare facilities. [13] However, sometimes the country experiences a serious shortage or lack of reagents, culture bottles and staff to meet the turnaround times for the culture results. Empiric antibiotics used are based on the age, comorbidities, condition of the patient and these are stipulated in the 6th edition of the Essential Drugs List and Standard treatment

guidelines for Zimbabwe (EDLIZ). [18] For example, according to the EDLIZ guidelines suspected cases of bacterial infections in neonates are treated empirically with a combination intravenous or intramuscular Gentamycin and Benzyl Penicillin or Cloxacillin. Other suspected cases of sepsis are treated empirically with Ceftriaxone and Chloramphenicol in both government and private healthcare facilities. [20] Empiric treatment should be changed when culture results are available and patients' outcomes could thus be affected by poor laboratory support.

Antibiotic prescribing remains a global challenge, as inappropriate prescribing will impact on patients' outcomes. In a study carried out in South African on antibiotic prescribing practices and their relationships to patients' outcomes in all South African intensive care units, Paruk et al (2012) discovered that inappropriate prescribing practices of antibiotics was associated with 27 % of deaths in ICU compared with 11% which was associated with appropriate prescribing practices. The authors concluded that inappropriate prescribing of antibiotics account for poor patient outcomes. [19]

International and national guidelines for prescribing antibiotics in healthcare facilities

Antibiotic prescribing in all healthcare settings is governed by international and national guidelines. The World Health Organisation developed an essential medicines list for all conditions in different healthcare settings. [20] These guidelines describe how drugs are to be prescribed in any condition and in any healthcare setting. They were also adopted by countries to develop their own essential medicine list which also include antibiotics. Zimbabwe used the WHO essential medicine list as a basis of the Essential Drug List of Zimbabwe (EDLIZ) first produced in 1981. These national guidelines are used to guide empiric prescription of antibiotics in healthcare setting in Zimbabwe, although the extent to which they are used has not been documented. The EDLIZ is revised every five years and was last revised in 2015. [18] However, in addition Zimbabwe has a body that also controls registration and prescribing of all medicines, called the Medicines Control Authority of Zimbabwe (MCAZ). The MCAZ protects humans and animal health by regulating accessibility of essential medicines, safe medical devices and effectiveness of good quality standards. [21] This study will determine whether prescribing practices are complying with national and international guidelines.

Factors influencing antibiotic prescribing behaviour

In a systematic review of 35 qualitative studies on understanding physicians antibiotic prescribing behaviour, Rodrigues (2013) reported that internal medicine physicians are the commonest prescribers of antibiotics in healthcare services. Their behaviour of prescribing is based on lack of knowledge, complacency, fear and a belief that they are not the ones causing antibiotic resistance.[22] Sanchez (2014) in his study on effects of knowledge, attitudes and practices of primary care providers on antibiotic selection in United States also explained that other factors which influence antibiotic prescribing include whether the patient had previous bacterial infection, severity of the illness, failure to follow guidelines and poor clinical practice and hence increased antibiotic resistance.[23] Surveillance of prescribing practices and determining the trends of resistance is of great importance as the data collected will contribute to the education of clinicians on patterns of resistant organisms and antibiotics they are resistant to. Auditing of antibiotic usage within a facility, feedback to the clinicians, and improvement of infection prevention and control practices should contribute to improvement of clinical outcomes. [3]

The role of infection control in combating antibiotic resistance

The WHO containment strategy for antimicrobial resistance recommended infection control as one of the interventions to contain antibiotic resistance, and hand washing was emphasised as it is the core element for infection prevention and control. Adherence to hand hygiene has proven to reduce transmission and acquisition of multidrug resistant organisms and other organisms that causes infections. [2] Therefore, infection control practices, when adhered to, reduce antibiotic resistance and improve patients' outcomes. However, a multidisciplinary and system oriented approach with effective leadership will be of great importance in developing surveillance systems of antibiotic resistance and monitoring of prescribing practices. [16]

Overuse of antibiotics and lack of adherence to infection prevention and control practices in hospitals and poor water supply, sanitation and hygiene in the community increases antibiotic resistance.[17] It is of paramount importance to strengthen infection control in human healthcare and biosecurity amongst animal health professionals and also in the community to reduce transmission of organisms that cause infections as well as multidrug resistant organisms within healthcare facilities and the community.[18]

Problem statement

Antibiotic resistance is a global challenge as most pathogenic bacteria are becoming resistant to antibiotics. Very few new antibiotics have been discovered in recent years and they are very costly to develop. Few healthcare facilities in Zimbabwe have antibiotic policies and guidelines if used are the 5th edition of the Essential Medicines List of Zimbabwe (EDLIZ). Although clinicians may use alternative guidelines such as those provided by WHO there are no publications describing which ones are used. [18]

Research aim

The study is aimed at describing and evaluating prescribing practices and describing compliance with the national and international guidelines on prescribing practices at a private hospital in Zimbabwe.

Research objectives

- To describe antibiotic prescribing practices for common infections in a private healthcare facility
- To identify susceptibility patterns of common pathogens in a private healthcare facility.
- To determine whether prescribing practices comply with national and international guidelines
- To determine factors associated with abnormal prescribing practices

Significance of the study

This study on surveillance of prescribing practices and trends of resistance is of great importance, as it will add to the body of knowledge and investigate the gap or lack of systems to monitor antibiotic prescribing practices, lack of data on resistance patterns, and lack of feedback to clinicians on resistance patterns. This study would benefit hospital management by raising awareness on antibiotic resistance and hence assist in the development of antibiotic stewardship programmes. As there is no surveillance system on antibiotics prescribing practices and trends of resistant pathogens in most of healthcare facilities, this study will inform the national antimicrobial resistance working group to design a surveillance network for all healthcare facilities in Zimbabwe. This study will also assist clinicians in knowing their local resistant pathogens and will contribute to the improvement of their prescribing of empirical treatment and hence improve patient outcomes.

CHAPTER THREE: METHODOLOGY

Study site

This study was carried out at Premier Service Medical Investments (PSMI) Westend, a private hospital in Harare, Zimbabwe. PSMI is comprised of several healthcare facilities (see Table 2)

Table 2: Types of health facilities and services under the umbrella of Premier Services Medical Investments.

Facilities	Number
Hospitals	6
Clinics	28
Laboratories	12
Rehabilitation centres	12
Emergency Rescue Ambulance services	10
Pharmacies	16
Optometry clinics	10

Westend hospital (WEH) is one of the hospitals. It has 120 beds and it offers medical care with a number of different units. (See Table 3)

Table 3: Different units at WEH and the number of beds

Units	No of beds
Intensive Care Unit	4
Neonatal units	12
Coronary	4
High Dependency Unit	14
Paediatric	14
Casualty observation	8
Maternity	28
Surgical	23
Medical	23
Accident and emergency	4 Resuscitation beds

Operating theatres	5 Operating rooms

WEH admits an average of 500 patients per month. This study was done in the critical care areas of the hospital in the intensive care unit, high dependence unit and neonatal unit and in the medical ward.

Study design

This is a descriptive cross –sectional study to reach the aim and the objectives of this study.

Duration of study

The study was done over 6 months' period from January to June of 2016.

Sampling framework

Number of patients admitted at this facility during the study period was 500 and target population for this study was all the patients admitted in the Intensive Care Unit, High Dependence Unit, Neonatal Unit and medical ward and who were on antibiotics over the period of the study. However, only 220 were included in the final analysis.

Table 4: Number of patients per wards under study

Ward	Numbers
Medical	121
High Dependency Unit	44
Neonatal Unit	35
Intensive Care Unit	20

Sample size calculation

Dobson's formula for sample size calculation was used in this study. It was based on 95% confidence interval and a 5% margin of error. [24]

Sampling method

(a)Investigation of prescribing practices

- Simple random sampling was used to select records of patients admitted in the critical care unit, neonatal unit and medical ward at this facility to determine those receiving antibiotic therapy.
- Convenience sampling of 50 specialists were picked out of the 250 specialists who admit at this facility was done and a questionnaire was administered to assess their prescribing practices. Out of the 50 specialists given the questionnaires only 16 responded.

(b) Surveillance of antibiotic resistance

Data on the susceptibility patterns for common pathogens isolated from blood cultures specimens processed from 2011-2015 was analysed. Data was retrieved from archived laboratory records, identification and susceptibility patterns were determined using manual phenotypic methods according to the laboratory standard operating procedures. Due to shortages of reagents isolates could not always be identified to genus and species levels and antibiotics were not given according to susceptibility patterns.

Inclusion criteria

Potential participants were included in the study if they were admitted to one of the study units as mentioned above, and if they received antibiotics during the study period. The specialists looking after those patients gave consent for their patient's records to be evaluated.

Exclusion criteria

Patients who did not receive antibiotic therapy were excluded, and those whose specialists did not give consent for records to be examined were not included in the study.

Data collection and analysis

Data collection tools

(a) A data collection tool was developed to collect data on patients' records that included demographics of age, gender, comorbidities, data from previous admissions, antibiotics prescribed in previous admissions, current antibiotic therapy and when prescribed, any

microbiological samples collected for cultures, results from the microbiology laboratory including species isolated, antibiotic resistance and susceptibility pattern. (see Appendix 1)

(b) To determine whether prescribing practices comply with national or international guidelines a questionnaire was also developed to collect data from the specialists regarding their antibiotics prescribing practices. (see Appendix 2**).** Questions included which guidelines were being used and whether the specialists comply with the gold standard rule of antibiotic prescribing that is to change antibiotics after culture results.

(c) Data was collected from blood culture results from 2011-2015 and was entered in a Microsoft Excel sheet with age, date when sample was collected, organisms isolated and susceptibility pattern.

Data entry and analysis

Data entry was done using Epi info version 7. It was then cleaned, coded and saved. Data was analysed using SPSS Version 20. Descriptive statistics was used to describe and summarize data, logistic regression analysis was employed to determine significant variables associated with antibiotic resistance. *P*-value and odds ratio outputs of the different variables tested were then compared. The variables tested for significance included age, gender, antibiotic regimen and duration of treatment, among other variables. The expected outcome was the proportion of patients with antibiotic resistance.

Ethical approval

Approval to conduct the study was obtained from the PSMI healthcare facility management, and ethical approval obtained from Medical Research Council of Zimbabwe (MRCZ/B/1096) and Health Research Ethical committee of Stellenbosch University (S16/04/070). Written consent was obtained from the doctors who completed the questionnaire on antibiotic prescribing practices, and data on antibiotic usage was collected from in patients' medical records and their laboratory results. Patient results were treated as strictly confidential with all data entry forms were identified by coded numbers. The data entry sheets were locked in a secure cabinet and all electronic entries were protected by use of a password.

CHAPTER FOUR: RESULTS

Antibiotic prescribing practice

Over the six-month period of prescription data was collected from patients admitted in ICU, NNU, High Dependency Unit and medical ward with a focus on the antibiotic prescribed to assess prescribing patterns. Figure 1 shows the age group of patients admitted to the wards over a period of the study. A total number of 220 patients were admitted over the 6- month period. The highest number of patients 68 (31%) admitted were between 21-30 years and the smallest number was 18 (8%) which is >51years

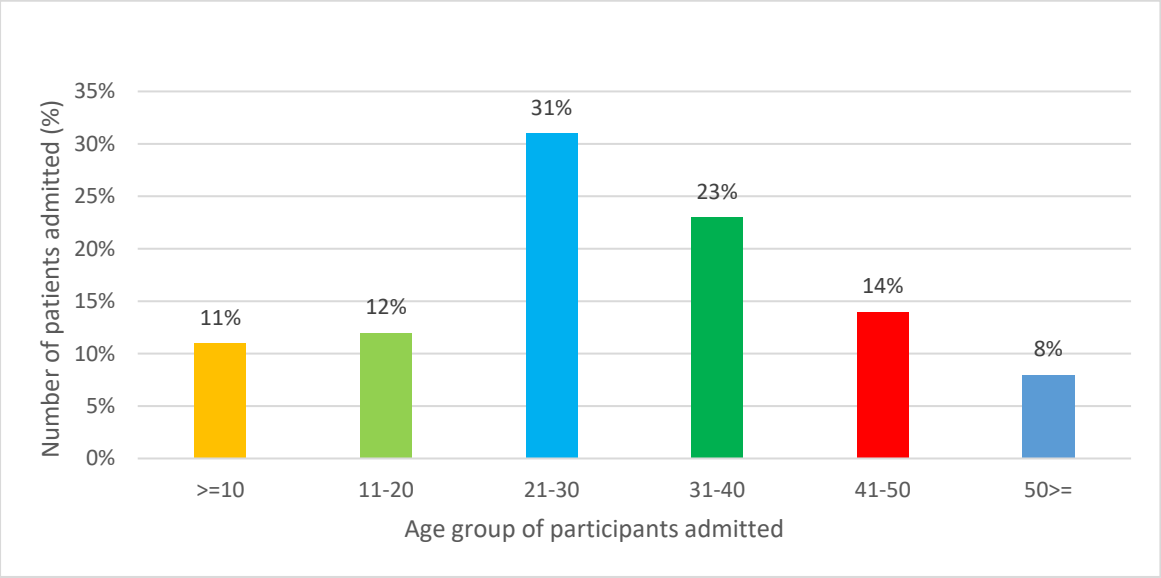

Figure 1: Age groups of the admitted patients (n=220)

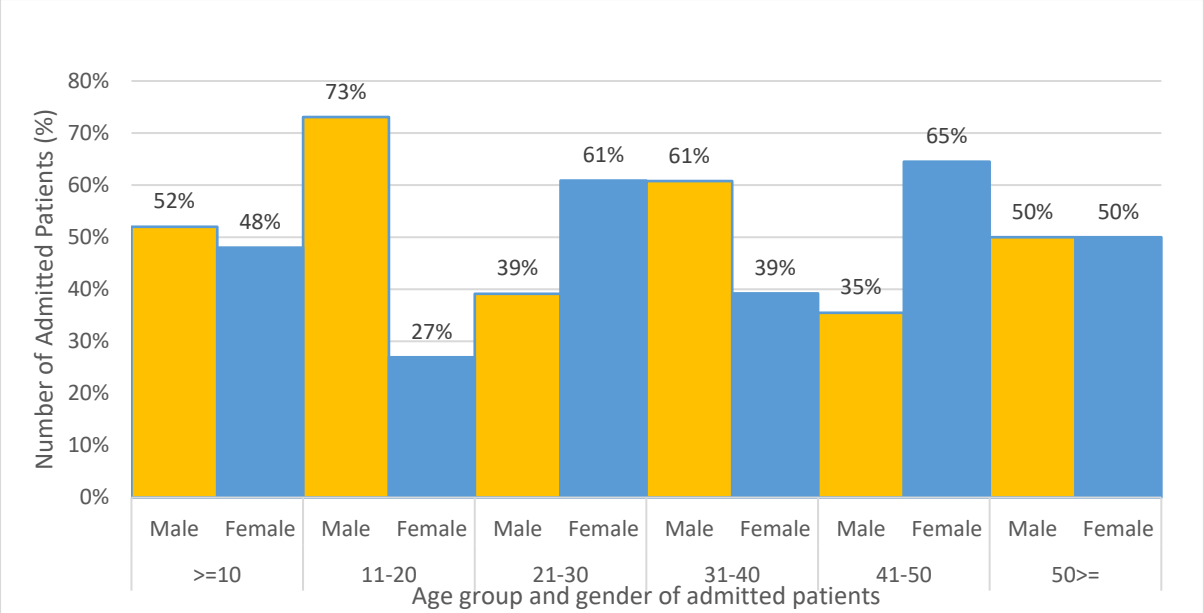

Figure 2: Gender and age groups of patients who had antibiotics prescribed

Figure 2: shows the distribution of gender, age and number of patients admitted. It has been noted that the sample comprises of 50% males and 50% females.

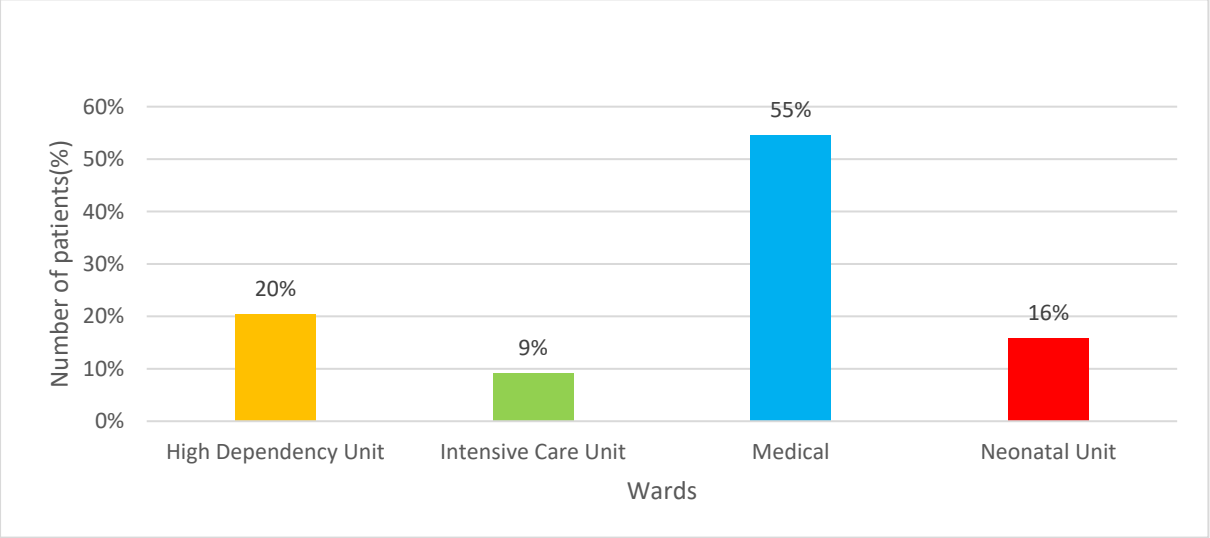

Figure 3: Number of patients admitted with antibiotics prescribed. (n=220)

As represented above, the medical ward had most patients 121 (55%) with antibiotics prescribed. The smallest proportion of patients 20 (9%) with antibiotics prescribed was in intensive care unit.

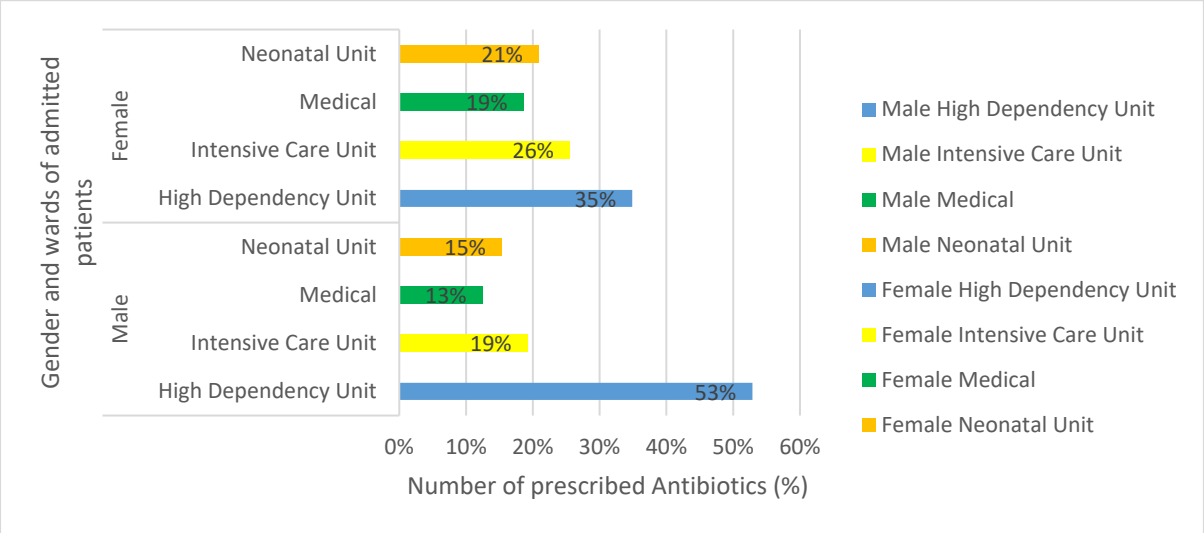

Figure 4: Number of antibiotics prescribed in percentage of total antibiotics prescribed in different units

Figure 4 shows the pattern of prescribed antibiotics to admitted patients in 4 different wards. It is clear that there are some cases where more than one antibiotic was prescribed to patients. The highest pattern of prescribed number of antibiotics was 5, prescribed to 18 patients and of the 220 patients 68 had 2 antibiotics, 16 had 3 antibiotics, and 3 had 4 antibiotics.

Prescribed Antibiotics	Frequency	Percentage
Ceftriaxone	176	56.59%
Metronidazole	55	17.68%
Azithromycin	5	1.61%
Benzyl Penicillin	5	1.61%
Gentamycin	16	5.14%
Cefaclor	1	0.32%
Augmentin	1	0.32%
Ciprofloxacin	8	2.57%
Ampicillin	2	0.64%
Clindamycin	5	1.61%
Doxycycline	2	0.64%

Roxithromycin	1	0.32%
Cloxacillin	8	2.57%
Meropenem	7	2.25%
Vancomycin	3	0.96%
Amoxicillin	16	5.14%
Total	311	100%

Table 5: Percentages of different antibiotics given to patients (n=220) prescribed antibiotics

The most commonly prescribed antibiotic was Ceftriaxone which was given 176 times (in 57% of cases receiving antibiotics). Metronidazole was prescribed 55 times (18%), Gentamycin and Amoxicillin 16 (5.14%) and 7 times (12%) respectively. Ciprofloxacin, Cloxacillin and Meropenem were prescribed at a lower percentage of 8-7% respectively, Azithromycin, Clindamycin and Benzyl Penicillin were the least prescribed. Most of the prescribed antibiotics were prescribed as combination with the other drugs especially Ceftriaxone.

Surveillance of common pathogens and antibiotic resistance from 2011-2015

Microbiological data on blood culture results from 2011- 2015 were reviewed in retrospect for the common pathogens and their susceptibility patterns. A total of 845 blood culture samples were collected and 667 had no growth obtained ,36 were contaminated and 142 had susceptibility results. The organism recorded with highest percentage was *Coagulase Negative Staphylococci* with resistance to almost all the antibiotics with 89.09% resistance to Cloxacillin. Lactose Fermenting Coliform was second and was also resistant to most antibiotics. Due to poor laboratory capacity, Lactose fermenting coliform was grouped instead of being specified. The private healthcare facility's laboratory had no proper machines and reagents to specify organisms, thus making it difficult to know the specific organisms classed as a "Lactose fermenting coliform".

Table 6: Identification and resistance pattern of 142 blood culture isolates collected from 2011-2015

Antibiotics:	Alpha-haemolitic streptococci	Coagulase Negative Staphylococcus	Escherichia Coli	Enterococci	Group D Streptococci	Lactose Fermenting Coliforms	Non-Lactose Fermenting Coliforms	Pseudomonas Aeruginosa	Staphylococcus Aureus	Staphylococcus Saprophiticus	Salmonella	Streptococci
Vancomycin	0.0%	72.4%	0.0%	3.5%	3.5%	3.5%	0.0%	0.0%	0.0%	0.0%	0.0%	17.2%
Meropenem	0.0%	66.7%	0.0%	0.0%	0.0%	16.7%	0.0%	0.0%	0.0%	16.7%	0.0%	0.0%
Cloxacillin	1.8%	89.1%	0.0%	0.0%	0.0%	1.8%	1.8%	1.8%	1.8%	1.8%	0.0%	0.0%
Imipenem	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Chloramphenicol	2.1%	23.4%	4.3%	0.0%	0.0%	21.3%	14.9%	19.2%	0.0%	2.1%	8.5%	2.1%
Ceftazadime	2.4%	69.1%	0.0%	0.0%	0.0%	21.4%	0.0%	4.8%	2.3%	0.0%	0.0%	0.0%
Tetracycline	10.2%	51.2%	5.1%	0.0%	0.0%	20.5%	5.1%	5.1%	0.0%	0.0%	0.0%	2.6%
Ceftriaxone	0.0%	70.3%	0.0%	0.0%	2.7%	0.0%	5.4%	16.2%	0.0%	5.4%	0.0%	0.0%
Erythromycin	1.7%	80.0%	0.0%	0.0%	1.7%	1.7%	0.0%	0.0%	1.7%	5.0%	0.0%	8.3%
Clindamycin	0.0%	66.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	33.3%
Gentamycin	0.0%	50.0%	2.8%	0.0%	0.0%	0.0%	0.0%	11.1%	0.0%	2.8%	0.0%	0.0%
Cotrimoxazole	3.0%	50.0%	0.0%	0.0%	1.5%	1.5%	13.6%	1.5%	3.0%	0.0%	1.5%	3.0%
Ciprofloxacin	1.6%	68.9%	0.0%	0.0%	0.0%	0.0%	1.6%	1.6%	1.6%	1.6%	0.0%	1.6%
Cefdinir	4.3%	78.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.1%	2.1%	0.0%	6.4%
Levofloxacin	0.0%	50.0%	10.0%	10.0%	10.0%	10.0%	0.0%	0.0%	0.0%	10.0%	0.0%	0.0%
Oxacillin	0.0%	88.9%	0.0%	0.0%	0.0%	3.7%	0.0%	0.0%	0.0%	7.4%	0.0%	0.0%
Norfloxacillin	0.0%	75.0%	0.0%	0.0%	0.0%	12.5%	0.0%	0.0%	0.0%	0.0%	0.0%	12.5%
Amikacin	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Ampicillin	0.0%	51.7%	3.5%	0.0%	0.0%	27.6%	6.9%	0.0%	0.0%	0.0%	10.3%	0.0%

Table 6 illustrates the pattern of antibiotics resistance for 12 organisms. Resistance to Vancomycin was noted in 5 organisms; 72% in Coagulase Negative *Staphylococcus*, 3.45% *Enterococci*, 3.45% Group D *Streptococci*, 3.45% Lactose Fermenting Coliforms and 17.24% *Streptococci.* Meropenem resistance was seen at a rate of 66.6% in Coagulase Negative *Staphylococcus* with least recorded in Lactose Fermenting Coliforms and *Staphylococcus. Saprophticus* (16.67%, 16.67% respectively). Cloxacillin has the highest resistance (89.09%) in Coagulase Negative *Staphylococcus* as compared to other organisms. There is no resistance recorded against Imipenem and Amikacin. Chloramphenicol showed some resistance to 9 out 12 organisms, with the highest percentage under Coagulase Negative *Staphylococcus* and Lactose Fermenting Coliforms (23.40 % and 21.28 % respectively). Ceftazidime showed resistance in 69% to Coagulase Negative *Staphylococcus*. The highest percentages of resistance

were recorded under the Coagulase Negative *Staphylococcus* on almost all antibiotics. Lactose Fermenting Coliforms as an organism was resistant to a large number of antibiotics.

Responses to the specialists' questionnaire

A questionnaire was sent to 50 specialists, of which 16 responded. The reason cited by the specialists for their lack of response was because being overwhelmed with ward rounds. The specialists see patients in several different healthcare facilities in Harare.

Table 7: Use of the national guidelines (EDLIZ) to prescribe antibiotics

Specialty	Use of the national guidelines (EDLIZ) to prescribe antibiotics				
	NO	OCCASIONALLY	SOMETIMES	YES	Grand Total
Anesthetist	100%	0%	0%	0%	(n=2)
Pediatrician	16.70%	0%	0%	83.30%	(n=6)
Physician	50%	0%	50%	0%	(n=2)
Physician (Internal medicine)	25%	25%	25%	25%	(n=4)
Physician (nephrologist)	100%	0%	0%	0%	(n=2)
Total	(n=7)	(n=1)	(n=2)	(n=6)	**(N:16)**

Of those that responded six were paediatricians, six internal medicine physicians, two nephrologists and two anaesthetists. Table 7 illustrates the poor adherence to the National guidelines EDLIZ except by the Paediatricians although 50% of General Physicians and 25% of Internal Medicine Physicians used them sometimes. The Anaesthetists and the nephrologist did not use them at all.

Table 8: Responses of doctors as to whether adding more antibiotics if patients are not responding to those prescribed

Adding more antibiotics to patients not responding to the ones prescribed without					
Specialty	NO	OCCASIONALLY	SOMETIMES	YES	Grand Total
Anesthetist	0%	0%	50%	50%	(n=2)
Pediatrician	16.7%	16.7%	33.3%	33.3%	(n=6)
Physician	0%	0%	0%	100%	(n=2)
Physician (Internal medicine)	50%	0%	25%	25%	(n=4)
Physician (nephrologist)	0%	0%	50%	50%	(n=2)
Grand Total	(n=3)	(n=1)	(n=5)	(n=7)	(N=16)

Table 8 above illustrates the percentages of doctors prescribing more antibiotics to patients. Their responses were measured on a 4-point scale that included "no", "occasionally", "sometimes" and "yes". The Anaesthetists were the most likely to add more antibiotics to patients who are not responding as their responses are distributed between sometimes and yes. The Paediatricians were varied in their responses with one not adding additional antibiotics. The two general physicians and the nephrologists added more antibiotics, two of the Internal Medicine physicians preferred not to add more antibiotics.

Table 9: Logistic regression results of independent variables to the trends of resistance

Trends of resistance	Coef.	Std. Err.	z	P>z	[95% Conf.Interval]	
Age	-0.006	0.012	-0.510	0.608	-0.029	0.017
Antibiotics prescribed	13.357	1092.659	0.010	0.000	-2128.215	2154.929
Sex	-0.477	0.320	-1.490	0.136	-1.105	0.150
Day of admission	0.074	0.047	1.580	0.114	-0.018	0.167
Previous admission	10.377	1092.659	-0.010	0.002	-2151.950	2131.195
Microbiological results	0.235	0.079	2.980	0.003	0.080	0.390
Comorbidities	2.621	0.598	4.380	0.000	1.449	3.792
National guideline	-0.563	0.359	-1.570	0.117	-1.268	0.141
Biological test	-0.365	0.501	-0.730	0.466	-1.348	0.617
Specimen	-0.045	0.152	-0.300	0.765	-0.342	0.252
_cons	5.173	1092.662	0.347	0.013	-2136.405	2146.750

The above logistic regression results show the impact of the independent variables to the trends of resistance. The model results report the coefficients, standard errors, z-values, probability values and the 95% confidence interval range of the calculated coefficients. Antibiotics prescribed are significantly related to the trend of resistance as the probability value (P>z =0.00) is less than 0. 005.Previous admission, microbiological results and comorbidities are significantly associated with resistance. The relationship shown in the table can be best summarized by the following equation:

Log (trend of resistance) = 5.173 - 0.006 x Age + 13.357 x Antibiotics prescribed - 0.477 x Sex + 0.074 x Day of admission + 10.377 x Previous admission + 0.235 x microbiological results + 2.621 x comorbidities - 0.563 x national guideline - 0.365 x biological test - 0.045 x specimen.

All the model coefficients are defined within the defined confidence interval range.

Table 10: Regression results reporting odds

Trends of resistance	Odds Ratio	Std. Err.	z	P>z	[95% Conf.Interval	
Antibiotics prescribed	12.965	7.221	4.600	0.000	4.352	38.623
Age	1.006	0.011	0.570	0.566	0.985	1.027
Sex	0.729	0.218	-1.060	0.290	0.406	1.308
Day of admission	1.051	0.043	1.230	0.220	0.970	1.139
Microbiological results	1.104	0.072	1.510	0.131	0.971	1.256
_cons	0.064	0.062	-2.840	0.005	0.010	0.427

Resistance is most likely associated with the prescribed antibiotics as the calculated odds ratio is greater than that of the other variables/factors. Age, Sex, Day of admission and Microbiological results had odds ratio which are in the same range [0-1.5] with corresponding probability values which are not significant at 0.05.

Summary of the results

1. This is the first study of this kind in a private hospital in Zimbabwe.
2. Inappropriate antibiotic prescribing due to no surveillance systems on antibiotic prescribing practice.
3. Limited adherence to use of national or international guidelines on prescribing antibiotics.
4. No policy for which antibiotics to test and which to report.
5. No feedback to clinicians and other healthcare workers on antibiotic resistance.

CHAPTER FIVE: DISCUSSION

Discussion

Surveillance of antibiotic prescribing practices and patterns of resistance of pathogens which causes common infections in healthcare facilities is of utmost importance as it reduces antibiotic resistance. [26] Guidelines informed by surveillance data provides more accurate information that assists clinicians in deciding which antibiotics to prescribe for empirical and prophylaxis treatment. In low income countries surveillance data on antibiotics prescribing practices and resistance patterns assists in informing interventions that will change poor prescribing practices and prioritising resources to those areas with resistance problems. It influences the planning, monitoring and evaluation of national antibiotic resistance guidelines.[16]

The findings of this study showed that most patients with antibiotic prescribed (55%) were in the medical wards, and this is where all physicians admit their patients most. Some (31%) of these patients had more than one antibiotic prescribed, and some (7%) had 3, (1%) had 4 and (8%) had 5 antibiotics prescribed. The most commonly prescribed antibiotic was Ceftriaxone, which was prescribed to 57% of the patients. On resistance patterns from blood culture isolates collected from laboratory records showed that most isolates tested were sensitive to Cloxacillin though it had highest level of resistance (89.9%) to Coagulase Negative Staphylococci.

A questionnaire was administered to Specialists to assess their adherence to national and international guidelines. Paediatricians were found to be using national guidelines 83.3% of the times when prescribing empiric and prophylaxis antibiotics.

In a systematic review of qualitative studies on understanding physicians' antibiotic prescribing behaviour Rodrigues (2013) investigated that physicians are the most known prescribers of antibiotics in healthcare service. [22] Similarly in our study it was observed that all physicians were major prescribers of antibiotics. Over prescribing of antibiotics is a global phenomenon, in our study we found out that more than one antibiotic was prescribed without microbial results and this increases antibiotic resistance. In a similar study carried out in India on prescribing pattern of antimicrobial agents in medicine Intensive Care Unit of a teaching hospital Badar and Nayale (2012) also discovered that more than one antibiotic was prescribed empirically to most of the patients in the ICU without microbial results hence increasing antibiotic resistance.[25] The most commonly prescribed antibiotic in our study was

Ceftriaxone prescribed to 57% of the patients and similarly the situational analysis carried out in Zimbabwe in 2017 showed that the most prescribed antibiotic in most healthcare settings was Ceftriaxone, and it has a high level of resistance to most common pathogens.[14] However inappropriate prescribing of antibiotics accounts for poor patients' outcomes thus long stay in the healthcare facility and eventually death. Paruk et al in her study on relationship of antibiotic prescribing patterns and patients' outcomes it was discovered that inappropriate prescribing patterns were associated with 27% of deaths in ICU compared with 11% which was associated with appropriate prescribing patterns [19]

Poor laboratory capacity is a very big challenge in low income countries as clinicians will end up prescribing antibiotics without microbial results. In this study very few patients had samples sent for culture and sensitivity, and on surveillance of common pathogens and antibiotic resistance, there was lack of proper machines and reagents to specify organisms and this impacts on the validity of its conclusion on antibiotic resistance. In a similar study carried out in Western Nepal Shankar et al also alluded poor laboratory capacity where a small number of patients had samples sent for culture and sensitivity and impacted on the validity of its conclusion on antibiotic resistance. [26] Findings of our study will be communicated to the clinicians as surveillance on prescribing practices and susceptibility patterns is of paramount importance; therefore, feedback to the clinicians is one of the ways to change their behaviour and reduce antibiotic resistance. In his consensus statement on strategies to prevent and control the emergence and spread of antimicrobial resistant microorganisms in hospitals, Goldmann et al identified development of a system which recognise and report trends of antimicrobial resistance within an institution. However, developing a system to rapidly detect and report resistant microorganisms in individual patients ensures rapid response by caregivers as some of the strategies to prevent and control antimicrobial resistance. [27]

Lack of national guidelines in Zimbabwe on antibiotic prescribing practices results in overprescribing of antibiotic, in our study an assessment on adherence to use of guidelines by clinicians was done. It was found out that most clinicians of different specialities prefer using international guidelines, except for the Paediatricians who are the only ones who use national guidelines 83.3% of the times. The WHO developed the essential medicine list which was also adopted by Zimbabwe and advised its revision especially with the knowledge of common pathogens and their susceptibility patterns. Therefore, all clinicians should use national

guidelines when prescribing antibiotics, as they are the ones that were found to be suitable for a low-income country like Zimbabwe.

The regression results of our study suggests that the antibiotic prescribing practices were influenced by several factors that were of statistical significance, namely antibiotics prescribed, history of admission, microbiological results and comorbidities. In a systematic review of qualitative studies on understanding physicians antibiotic prescribing behaviour, Rodrigues (2013) similarly identified that health systems are associated with inappropriate prescribing of antibiotics directly and indirectly. Direct factors are through policies and guidelines in place and indirectly by the pressure of institutions to push volumes of patients based on trust that antibiotics prescribed will reduce complications or lose of the patient. [22]

CHAPTER 6 RECOMMENDATIONS AND CONCLUSION

Based on the findings of our study the following is recommended

- Development of a surveillance system on antibiotic prescribing practices and susceptibility patterns of common pathogens that cause infections.
- Monitoring adherence to use of national guidelines when prescribing empiric and prophylaxis antibiotics
- Formation of a therapeutic committee which will monitor and control antibiotic prescribing practices and give feedback to clinicians through the advisory board.
- To source for funding to improve laboratory capacity.
- Reviewing of antibiotic prescribing policies and giving feedback to prescriber

Limitations

The investigator collected data on her own as there were no trained people who know about data collection, this was very difficult for the investigator as she normally works out of town where the facility was situated. Due to economic instability patients were no longer admitted in private hospitals, which made it difficult to reach a sample population of 500 patients. The investigator finally sampled 220 though they were of statistical significance. Blood cultures were not done when patients were commenced on antibiotics due to economic constraints within the country procurement of culture bottles was erratic. Poor laboratory capacity which includes shortage of reagents, machines to specify organisms led to no identification of organisms from genus to species levels. Lack of drugs to test susceptibility patterns of gram-negative bacteria and gram- positive bacteria led to testing susceptibility patterns with what was available. There was poor response of specialists to the questionnaires due to hectic schedules of the nature of their job. Lastly lack of funding for the investigator to properly carry out the study.

Conclusion

Surveillance of prescribing practices and common pathogens susceptibility patterns are of paramount importance, as it provides information which assist clinicians in deciding which antibiotics to use for empirical and prophylaxis treatment. In low income countries surveillance data assists in prioritising resources to those areas with resistance problems. Policy makers should come up with polices which regulates prescribing of antibiotics and adherence to national and international antibiotic prescribing guidelines. As there is paucity of data on antibiotic prescribing practice, common pathogens and their susceptibility patterns in healthcare facilities in Zimbabwe this study will add on data to national health system and assists in the development of national antibiotic policy and antibiotic stewardship programmes.

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APPENDIX 1 – DATA COLLECTION TOOL

Part A

Ward

Patient hospital number

Age

Sex

Date of admission

Diagnosis

Previous admission: yes no

Antibiotics prescribed on previous admission: yes no

Microbiological results from previous admission

Any trends of resistance

Comorbidities

Prescribed antibiotics

Date started Dose Route of administration frequency change of route of admin.

Date stopped

PART B

How where antibiotics prescribed: Yes NO

Empirically

Using national guidelines (EDLIZ)

Using bacteriology tests

Any other guidelines used

PART C

Number of antibiotics given

Any bacteriology tests done

If yes which one and was this collected before antibiotics were started

Bacteriology results

Did treatment change after the bacteriology results?

Any trend of resistance noted

APPENDIX 2 - DOCTORS' QUESTIONNARE

Part A

Serial number

Specialty

Ward

Part B

Is there a system that control antibiotic prescribing at this health care facility?

If yes which one

Do you use the national guidelines (EDLIZ) to prescribe antibiotics?

Do you do bacteriology tests before prescribing antibiotics?

Do you change antibiotics according to the bacteriology results?

Do you add more antibiotics to patients not responding to the ones prescribed without bacteriology tests?

Do you check for resistance patterns if your patient is not responding to treatment?

What other guidelines do you use to prescribe antibiotics?